



CONCEPT PAPER

ON THE DEVELOPMENT OF FURTHER GUIDANCE AROUND MEDICATED PREMIXES

Introduction

At the tenth VICH Outreach Forum, the subject of guidance on medicated premixes and their application in feed was put forward. As a result, the current VICH guideline on medicated premixes (GL8) was reviewed by the topic leader (Japan) and a draft discussion paper was prepared by AnimalhealthEurope on whether further guidance on medicated premixes could be appropriate.

In a follow up of that discussion at SC 37, AnimalhealthEurope was asked to prepare a clarified discussion document. After SC 38, the Discussion Document was approved by the Steering Committee per email on 27 March 2020. Afterwards, a Task Force on Medicated Premixes was nominated to write a Concept Paper before the November 2020 Steering Committee, on the development of further guidance around medicated premixes.

The 38th Steering Committee asked to review the current VICH guidance on medicated premixes and to identify where additional guidance on medicated premixes could be given. Therefore, it is clear that the updated or new guidance would only pertain to medicated premixes and would not be about registration requirements of medicated feed as such.

In the various VICH regions*, different definitions are being used when referring to the Medicated Premixes that are included in this concept paper. Therefore, it is important to review the definitions used in this paper and the VICH regions:

- **Medicated premix (also called “Type A medicated article” in USA or “drug premix” in Canada)** (in scope):

A veterinary medicinal product consisting of a mixture of one or more drug substances (generally with a carrier), that is prepared to facilitate oral administration of the drug to animals when mixed with feed (see definition in VICH GL8).

Medicated premixes for liquid feed are also in scope.

Geographic Region	EU + OUS	USA
Veterinary Medicinal Product	Medicated premix	Type A medicated article
Medicated feed	Medicated feeds or feedingstuffs	Type B/C medicated feeds

Table 1: comparative terminology in VICH regions

- **Feed additive** (out of scope):
Additives used in feeds for non-veterinary uses (specified by each country/region).
Such additives are not considered to be veterinary medicinal products and will be out of scope.

* VICH Regions: the VICH members (Japan, USA and European Union) and the VICH observers (Canada, Australia, New Zealand and South Africa)

- **Medicated feed:**
Feed containing medicated premixes. Such medicated feed is mostly not considered to be a veterinary medicinal product and will be out of scope of this guidance.
- **Medicated drinking water and topdressing formulations**
Oral formulations (like oral powders) not intended for inclusion in medicated feed are out of scope.

Problem Statement, including technical and legislative requirements in the different regions

The starting point for future work is already embedded in VICH guideline 8, which identifies indeed some gaps in its guidance to be filled at a later stage, by stating that *“Other stability studies which might be important to consider, like stability in relation to conditioning and pelleting, segregation and homogeneity studies are not within the scope of this guideline.”*

The request as formulated by VOF is broader than just the premix stability study, but also asks for broadening the focus of VICH GLs to include other requirements/data that are critical when assessing dossiers for medicated premixes. So, apart from the fact that technical requirements for medicated premixes are incomplete, the VOF called as well for technical requirements for medicated premixes that refer to a premix’s suitability for use in the preparation of medicated feed.

Current technical and legislative requirements in the VICH guidelines

GL3 Stability testing of new veterinary drug substances and related finished products

GL 3 contains just one reference to medicated premixes (in the scope paragraph, page3):

“Further guidance on new dosage forms, medicated premixes, and on biotechnological/biological products can be found in VICH guidelines GL4, GL8, and GL17, respectively. Stability testing following first use of the product (e.g., first broaching of a vial) is not covered within this guideline.”

GL4 (an annex to GL3) Stability testing for new vet dosage forms

This GL relates to “what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.”

...“Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time may be acceptable in certain justified cases.”

There is however no direct mentioning of medicated premixes in this guideline.

GL17 Stability testing of new biotechnological/biological veterinary medicinal products

This guidance does not contain any info on medicated premixes.

GL58 Stability Testing of New Veterinary Drug Substances and Medicinal Products in Climatic Zones III and IV

This new guidance covers stability test parameters to be used for climatic zones III and IV.

Obviously, this guidance is not yet referenced in the existing guideline 8.

GL8 Stability testing for medicated premixes

This guidance, building on GL3, covers stability test parameters to be used for long-term and accelerated testing with medicated premixes in climatic zones I and II. It does request the testing to happen typically in the final packaging material, although smaller pack sizes can be justified. Evidence is only required to demonstrate the stability of the Medicated Premix before incorporation into an additional feed.

In the introduction of GL8, we read: “This document ... addresses the recommendations for stability testing of veterinary medicinal Medicated Premix drug products. The parent guideline (VICH GL3) provides a general indication of the information on product stability generated, but the annex for Medicated Premixes leaves sufficient flexibility to encompass a variety of different practical and scientific considerations that are specific to the characteristics of the drug products being evaluated. Other stability studies which might be important to consider, like stability in relation to conditioning and pelleting, segregation and homogeneity studies, are not within the scope of this guideline (8).”

[Overview of the current technical and legislative requirements in the different VICH regions.](#)

In general, we see a different level of requirements depending on the region and the local regulations (e.g. the definitions feed-additive vs medicated premix). We focus here on what is required when submitting a dossier for a Medicated Premix.

Japan:

- Only type A medicated articles (veterinary premixes) are regulated as VMPs.
- They need to follow VICH GL8

Canada:

- Stability of the medicated premix
- Samples for analysis
- Homogeneity and segregation of the medicated feed mix
- Feed assay validation, including attention for interference via concurrently used other medicines/products
- 3 months stability of the medicated mashed and/or pelleted feed
- Premixes proposed for concurrent use

Australia:

- VICH GL8 except the testing conditions for real time storage.
- VICH GL45 Bracketing and matrixing and VICH GL51 statistical evaluation when applicable
- In-feed stability for medicated premix administered via liquid feed

EU:

- Notice to Applicants vol 6B, p 53, 2G describes the information required for medicated premixes:
 - *Other Information: For medicated premixes (products intended for incorporation into medicated feedingstuffs), information shall be provided on:*
 - *Inclusion rates,*
 - *Instructions for incorporation,*
 - *Homogeneity in-feed,*
 - *Compatibility/suitable feedingstuffs,*

- *Stability in-feed, and the proposed in-feed shelf life,*
 - *A specification for the medicated feedingstuffs, manufactured using these premixes in accordance with the recommended instructions for use*
- *More information is given in the Note for Guidance on additional quality requirements for products intended for incorporation into animal feeding-stuffs (medicated premixes) (EMA/CVMP/080/95)*

USA:

- Type A medicated articles (veterinary premixes) are regulated as VMPs and are expected to follow VICH GL8 guidance.
- Core CVM Guidance For Industry is GFI #5 Drug Stability Guidelines as it provides an overview of the requirements.
- Other requirements (outside of VICH GL 8) include:
 - In-feed stability in different feed-types, including the impact of various manufacturing processes (i.e. pelleting, extrusion, etc.) used for medicated feeds
 - Homogeneity and segregation of the Type A Medicated Article and representative Type B and C Medicated Feeds manufactured from it including mixability in feed, and homogeneity and segregation (during transportation over a distance of 50 miles)
 - Feed assay validation
 - In different feed types
 - Evaluation of interference, i.e., method specificity, with respect to other drugs commonly used in feeds
 - Feed assay method transfer trial to independent labs
 - Stability studies of Type B and C medicated feeds are driven by typical use patterns and expiration dates may be required if the feeds are not stable for the typical period of use.

Anticipated benefits

For Industry and other interested parties

Clear and harmonized guidance on technical requirements are essential to enable global development of veterinary medicinal products, including medicated premixes.

Development of additional requirements in Guideline 8 on stability data for medicated premixes will provide opportunity to develop a harmonized dossier for submission in VICH regions as well as in VICH Outreach Forum countries.

Reducing discrepancies in requirements between the Member regions will provide more opportunity to develop the medicated premixes for more global markets, which would increase the availability of this important pharmaceutical form.

For Regulatory Authorities

If the requirements for medicated premixes were harmonized across VICH, the original dossier would be much more likely to be in compliance with requirements which would not only result in less use of resources but also in an increased efficiency as fewer questions are to be expected.

Within VICH Outreach regions, Regulatory Authorities look to VICH to understand what appropriate requirements would be for veterinary products. However, they cannot find a global guideline that addresses most of their questions on the requirements for medicated premixes. If more guidance is developed by VICH on medicated premixes, harmonized guidance on aspects such as for instance homogeneity or segregation would be available for VICH Outreach regions.

Impact for public health, animal health and animal welfare.

Veterinary medicated premixes are an important element of administering veterinary medicines to farm animals that are raised and kept in groups.

This use is global and across the veterinary community, authorities and animal health industry.

The feed route can deliver a reliable and consistent dose of veterinary medicines to the farm animal and this dose is determined and approved to be safe and effective by the regulatory authorities as part of the product licence for the veterinary medicated premix, which is developed and formulated for use in feed. Especially for antibiotics, and antiparasitics this route of administration is widely used.

Although other routes of administration are also available, such as injection and drinking water use, the feed route needs to be an option for farmers and vets due to the ease of administration as they seek to maximise animal health and welfare on their farms.

Additionally, medicated feed may be an option for companion animals by enabling long-term treatment in a regular feed.

Discussion

Depending on the region a Medicated Premix could be described differently as a Type A Medicated Article (USA) and medicated feed (feed containing medicated premixes could be described as Type B or Type C Medicated Feeds (USA)). In this Concept Paper only the terms “medicated premix” and “medicated feed” will be used. Aligned with VICH guideline 8, medicated feed will be out of scope of this concept paper, unless directly linked to the in-use aspects of the medicated premix (as discussed below in the mandate proposal).

The definition of what is to be considered a (non-veterinary) feed additive and what should be considered a medicated premix can be different depending on the region. That distinction will be kept out of the discussion as it is a local or regional competency.

Nevertheless, if a region considers a certain product type to be a medicated premix, the technical requirements for medicated premixes in VICH regions are applicable. On the other hand, when a certain product type is legally considered a non-veterinary feed additive in a region and therefore out of scope of VICH guideline 8, it would also be out of scope for this concept paper.

VICH Guideline 8 has been published by the VICH Steering Committee for step 7 on 16 November 1999 as an annex guideline to parent guideline 3 (Stability testing of new veterinary drug substances and medicinal products). Overall, all VICH member regions (and most VICH observers) apply fully the requirements in VICH Guideline 8 to medicated premixes dossiers in their region.

The following requirements have been put forward in VICH GL#8:

- Medicated Premixes are recommended to be tested at 25°C ± 2°C / 60% RH ± 5% (long-term testing) and 40°C ± 2°C / 75% RH ± 5% (accelerated testing) and with the same schedule intervals as described in the Parent Guidance (GL3). Other storage conditions are allowable if justified.
- Where "significant change" occurs due to accelerated testing, additional testing at an intermediate condition e.g., 30°C ± 2°C / 60% RH ± ±5% should be conducted. "Significant change" at the accelerated condition is defined as failure to meet specifications.
- Evidence is necessary to demonstrate the stability of the Medicated Premix before incorporation into an additional feed.
- The shelf-life specification of a Medicated Premix should include necessary stability indicating test parameters.
- The testing should be carried out in the final packaging proposed for marketing when practicable. The use of smaller comparable containers simulating the actual market packaging may be justified.

In the introduction to Guideline 8, the authors mention that *"The parent guidance (VICH GL3) provides a general indication of the information on product stability generated, but the annex for Medicated Premixes leaves sufficient flexibility to encompass a variety of different practical and scientific considerations that are specific to the characteristics of the drug products being evaluated. Other stability studies which might be important to consider like stability in relation to conditioning and pelleting, segregation and homogeneity studies are not within the scope of this guidance."*

In most of the VICH Member regions, specific requirements, such as those mentioned in the GL8 introduction, that focus on the technical characteristics that define the suitability of the medicated premix to be used in a medicated feed are also put forward.

These requirements cover (amongst others):

- The technical characteristics of a premix in terms of:
 - Homogeneity of the medicated premix and homogeneity of the medicated feed, including mixing and blending,
 - Risk of segregation (during storage and transport),
 - Impact of preparation of medicated feed (extrusion, expansion, mashing, pelleting) on the stability of the active ingredient from the medicated premix
 - Potential interactions with certain feeds or feed types
 - Stability after opening of the primary packaging (in use stability)
- Analysis of the active ingredient in the medicated feed after inclusion of the medicated premix
 - Validation of the assay in different feed types
 - Transferability of the analytical method to other, independent labs
- Suitability of the medicated premix to manufacture a medicated feed with sufficient shelf life

These technical requirements indicate if a medicated premix is suitable to serve its purpose (mixing to prepare a medicated feed), and have not yet been addressed by the current Guideline. At the same time, the VICH Outreach Forum Countries, looking towards VICH guidance to find models and templates, have expressed their need for this additional guidance.

Obviously, the update of VICH guidance on medicated premixes must also take into account the insights of newer stability related guidelines such as GL58 on stability testing for climatic zones III and IV, GL45 on bracketing and matrixing or GL 51 on statistical evaluation including extrapolation of results of stability studies on medicated premixes.

Any additional guidance should be focused on the medicated premix in all its complexity, including the technical requirements that define if a medicated premix could be suitable and fit to later be mixed into a medicated feed.

It needs to be clear however, that in no way this would set any rules for the registration of medicated feed. Such guidelines are to be developed independently according to the local or regional rules.

Recommendation

As seen in several regions, more guidelines have been or will be developed for medicated premixes, outside of the VICH-agreed test parameters for medicated premixes in GL8.

The current GL8 only covers part of the test parameters for stability studies with medicated premixes.

This concept paper proposes to create an Expert Working Group (EWG) that should focus on the technical requirements for medicated premixes.

The EWG should have two major tasks in its mandate.

A first mandate will be to **review and update VICH GL8** to include:

- a. **Zone III, Zone IV A and Zone IV B** (ref to GL58 and GL3(R))
- b. **In-feed stability** for the intended **medicated feed must also be covered** (using different feed types). Pelleting and/or extrusion stability must be covered in this point.
- c. **Stability** of the premix **after opening of the primary packaging**
- d. **Bracketing and matrixing** (referring to GL 45) **or statistical evaluation (reference to GL 51) including extrapolation** of results of stability studies on medicated premixes
- e. Additional stability considerations for a **liquid premix**

In a second mandate, the EWG should **develop a concept paper on the necessity and feasibility** of guidelines covering other technical requirements for premixes (such as amongst others):

- **Analytical method validation** (reference to existing VICH guidance, including GL39) and sampling methodology in the premix and in feed
- **Homogeneity and segregation** studies for premix and medicated feed under normal storage and transport conditions

Timetable and milestones

The first mandate should be relatively easy and should be leading to a revision of GL8 at step 4 at the “next” Steering Committee (SC) in November 2021 or by written procedure.

- Concept paper to be finished before the November 2020 Steering Committee (September 2020, by written procedure)
- Step 1: Expert Working Group formed out of the Task Force and Topic Leader and Chair of EWG (September 2020)

- Step 2: Draft guideline 8R to SC by end July 2021 (one face to face meeting is foreseen to finish this draft and to allow in depth discussions for the second mandate)
- Step 3: SC releases for public consultation at SC 40 (Nov 21)
- Step 4: Public consultation until May 2022
- Step 5: Revised GL8R ready for SC by August 2022
- Step 6: SC approves GL8R at SC 41 (Nov 2022)

For the second mandate, the EWG should finish the initial assessment and recommendations for additional topics and guideline development, resulting in a concept paper by end July 2021 which is three months before the November 2021 Steering Committee.

Further timeline for the second mandate will be depending on the approval of the second concept paper.

Impact assessment for Industry

- a. Clarity and global consistency of requirements for medicated premixes, including VOF regions
- b. Reduction in number of studies needed for global marketing
- c. Increased regulatory predictability and potential market for the same dossier

Impact assessment for Regulatory Authorities

- a. Increase in clarity of requirement (less uncertainty expressed by Industry)
- b. Decrease in submission of failed studies or dossiers
- c. Increase in consistency of studies and dossiers
- d. Increased availability of medicated premixes

References to literature, existing relevant international guidelines or standards

EU:

- REGULATION (EU) 2019/4 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) No 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC
- Monograph of the European Pharmacopoeia on “Premixes for Medicated Feeding stuffs for Veterinary Use”. 01/2014: 1037
- EU Guidelines: Note for Guidance: Additional quality requirements for products intended for incorporation into animal feeding stuffs (medicated premixes) (EMEA/CVMP/080/95-Final)
- EU Guidelines: Position paper on premixes for medicated feeding stuffs for veterinary use versus powders/granules for oral use or use in drinking water. (EMEA/CVMP/199/97-Final)

Canada:

- Guidance for industry: Preparation of veterinary new drug submissions, Veterinary Drugs Directorate, Health Canada (version 1.1, March 2007)
- Guidance for Industry - Preparation of Veterinary Abbreviated New Drug Submissions - Generic Drugs, Veterinary Drugs Directorate Health Products and Food Branch (December 2009)
- Guidance Document Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines - Veterinary Drugs (GUI-0012) (May 2011)
- Guidance Document Post-Notice of Compliance (NOC) Changes: Quality Document, Health Canada (June 2019)

USA:

- CVM Guidance For Industry (GFI) #5 Drug Stability Guidelines
- CVM GFI #23 Medicated Free Choice Feeds – Manufacturing Control
- CVM GFI #135 Validation of Analytical Procedures for Type C Medicated Feeds
- CVM GFI #136 Protocols for Conduct of Method Transfer Studies for Type C Medicated Feed Assay Method
- CVM GFI #137 Analytical Methods Description for Type C Medicated Feeds